**PHARMACOKINETICS OBJECTIVES**

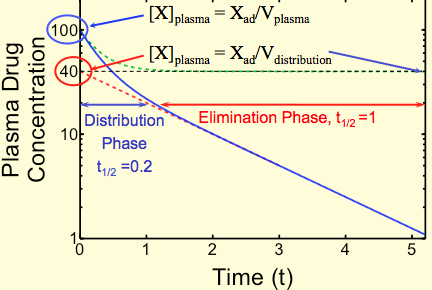
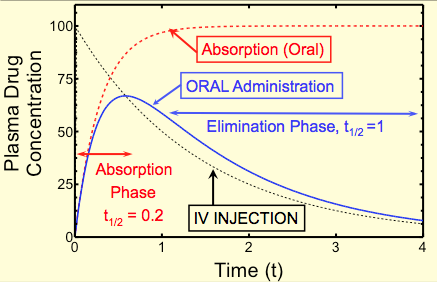
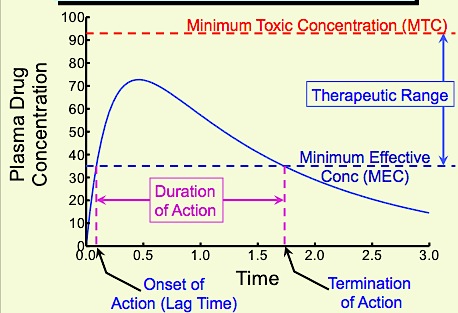
1. Recognize that the variation in plasma drug concentration with time is a complex function of the rates of absorption, distribution and elimination
   1. The change in concentration of drug X in the blood with time = d[X]blood/dt = Absorption rate – Distribution Rate – Rate of Elimination
      1. Or d[X]blood/dt = ka([X]a – [X]blood) – kd([X]blood – [X]t) – (ke1 + ke2)[X]blood
2. Describe the general properties of a first order process, including half-life, linearity of semilog plot, and how long it takes for the process to be “complete”.
   1. First-order elimination—rate of elimination is proportional to the drug concentration (i.e. constant fraction of drug eliminated per unit time)
      1. d[X]/dt= -ke \* [X]
         1. the rate of decrease in the blood concentration is proportional to the drug concentration in the blood
      2. [X]t = [X]0 \* (e-ke\*t)
   2. t ½
      1. plots of drug concentration vs. time exhibit an exponential decay –characterized by half life
      2. **ke\*t ½ = ln2 = 0.69**
      3. it takes 4-5 half lives to eliminate a drug from the body ~95% is gone
      4. tell us how long it will take for the concentatino of drug in the patients blood to fall to 50% of its current value (after administration has stopped)
      5. First Aid
         1. t1/2 = (0.7 \* Vd)/ CL
   3. linearilty of semilog plot
      1. if you graph the log[drug] vs. time you get a straight line
         1. 
      2. slope = ke/2.3
3. Estimate the half-life of a drug from data or graphs relating plasma drug concentration and time
4. Define clearance (CL) in terms of first-order drug elimination
   1. CL: Relates the rate of elimination to the plasma concentration
      1. = rate of elimination of drug/plasma drug concentration= Vd x ke (elimination constant)
         1. since ket1/2 = 0.69 then…
         2. CL= 0.69\*Vd/t1/2 and
         3. **t1/2 = 0.69\*Vd/CL**
         4. SOOOOOO if you vary the Vd  only the half life changes (↓ Vd then ↓ t1/2 and ↑ ke) not the CL
      2. **Rate of elimination (g/min) = CL \* [X]blood**
         1. \*\*don't forget to make sure your using the same units
         2. Rate of Elimination depends only on plasma free drug concentration and the clearance
   2. CL is ONLY dependent on the intrinsic ability to eliminate a drug and is **independent of Vd** 
      1. Both ke and t1/2 are **dependent on Vd**
   3. Need to find total clearance (each pathway of elimination has a specific clearance) so add up CLkidney + CLliver + CLother 
      1. Knowing the CLtotal allows one to calculate the rate of elimination for the desired [Drug]blood
         1. **Rate of elimination (g/min) = CL \* [X]blood**
         2. **Rate of elimination determines the dosage necessary to maintain the desired drug concentration in the blood (RE determines dosage rate)**
5. State the relationship between rate of elimination (RE) and clearance and explain its utility
6. State the relationships between CL, k, half-life and volume of distribution (Vd)
7. Explain why some drugs exhibit non-first order or saturable elimination and explain the effect this has on the relationship between the RE and plasma drug concentration, and how this gives rise to “dose-dependent CL”.
   1. Zero order process
      1. X0= 1 so rate = k [X]0 = k
      2. Rate is **independent of pressure/concentration**
      3. Process gets sarurated (has enzymes that metabolize drug or transport it)
      4. Ex: PEA (looks like an “0”—zero order)
         1. Phenytoin
         2. Ethanol
         3. Aspirin (at high or toxic concentrations)
   2. Non first order elimination will be observed in processes that depend on enzymes/pumps (these can become saturated) and can exhibit Michaelis-Menton kinetics (i.e. Ratemax)



* + 1. For these at low doses will behave as first order but approach zero order at higher doses
    2. Blood levels of drug eliminated by zero order kinetics are more difficult to control
    3. Aka capacity-limited, saturable, dose or concentration dependent, non-linear or Michaelis-Menton elimination

1. Define zero-order elimination
2. Recognize that absorption is often a first order process
   1. Absorption is the process by which the drug gets from the site of administration into the blood stream
      1. IV drugs bypass absorption
   2. Drug therapy is monitored by measuring the concentration of the drug in the blood stream
      1. Absorption leads to an ↑ in plasma drug concentration
         1. Can be approximated by a first order process
   3. 



1. Recognize that distribution is often a first order process
   1. Distribution is the process by which the drug moves from the blood to the various tissues and organs of the body
   2. It is monitored by measuring the concentration of the drug in the blood stream
      1. Can be approximated by a first-order process
      2. Leads to a ↓ in plasma concentration of drug
         1. This decrease is more evident for drugs given IV or if absorption is extremely rapid
      3. Distribution stops when the concentration of drug is same in all the aqueous environments of the body
2. Describe the characteristics of the plasma concentration-time curve for a drug given as a single bolus IV dose in terms of a two compartment model, distribution and elimination and how the Vd may be determined from this data.
   1. 
   2. If you give a single IV bolus it is injected into the blood (no absorption) and then the plasma concentration decreases as the drug isnt being distributed to the tissues and extracellular space (distribution phase) and then it further ↓ do the the elimination of the drug (elimination phase)
   3. if you extrapolate the elimination phase line it goes to 40 and that gives you the [X]blood
      1. you then just plug it into the [X]plasma = Xad/Vd ­so V­d = Xad /[X]plasma
3. Describe the characteristics of the plasma concentration-time curve for a single dose of a drug given by oral or other non-IV route in terms of one compartment, absorption and elimination. 
   1. The peak is reached when absorption rate declines and elimination rate rises and the two rates become equal
   2. In the graph the absorption phase slightly delays elimination compared with the same dose give IV because the entry of the drug into the blood is delayed
4. Describe the significance of the area under the plasma drug concentration-time curve (AUC) for a single dose of a drug and explain how it is related to dose, clearance and bioavailability, and how AUC measurements can be used to determine bioavailability.
   1. **AUC = Dose \* bioavailability (f)/ CL**
      1. AUC depends on dose and CL
   2. AUC is a product of concentration and time and often used as an overall measure of the exposure of the patient to a drug
      1. If CL was 0 exposure would be infinite
      2. If CL was infinity then exposure would be 0
      3. If CL and f are constant than AUC is proportional to the dose irrespective of the route of administration or rate of absorption
      4. With IV drugs bioavailability = 1 so f=1
      5. SO foral­­/fIV = AUCoral/ AUCIV
         1. If fiv= 1 then foral = AUCoral/ AUCIV
            1. So foral can be determined by comparing the AUC for a dose of drug given orally with a dose administered IV
            2. AUC will be equal is absorption is complete and the CL is the same
5. In relation to the plasma drug concentration-time curve for a single dose of a drug define the terms Cmax, Tmax, minimum effective concentration, minimum toxic concentration, therapeutic range, onset of action, termination of action, duration of action and how these affect selection of drug dose.
   1. 
   2. Cmax-maximum plasma concentration seen following a single dose
   3. Tmax- the time it takes to reach Cmax
   4. Minimum effective concentration-- the plasma drug concentration below which there is no clinical benefit
   5. Minimum toxic concentration—The plasma drug concentration above which toxic effects are seen
   6. Therapeutic range—plasma drug concentrations between MEC and MTC
   7. Onset of action—the time after the administration of the drug when it reaches the MEC
   8. Termination of action—When the drug falls below the MEC
   9. Duration of action-time for which the drug concentration is above the MEC
      1. Is not the same as how long it takes for the drug to be eliminated
6. Explain how Cmax, Tmax, AUC and elimination half-life are affected by changes in drug dose, clearance, and rate of absorption.
   1. Dose
      1. Cmax and AUC are proportional to dose
      2. Tmax is independent of dose
      3. Half-life is independent of dose
      4. OOA is inversely related to dose
      5. TOA increases with dose
      6. DOA increases with dose but because it depends on the MEC DOA is NOT proportional to dose
   2. CL (as clearance ↑…)
      1. AUC ↓
      2. Cmax ↓
      3. T max ↓
      4. Half life ↓
      5. TOA occurs sooner but with little effect on OOA
      6. DOA ↓ and will reach zero when Cmax fails to exceed MEC
   3. Rate of Absorption
      1. OOA and TOA will be quicker in a drug given IV (no absorption) and Tmax will be quicker
      2. Cmax will be lower for a drug given orally vs IV (even is bioavailability is 100%)
         1. Toxic effects are MORE LIKELY WITH IV administration
      3. DOA of a drug given IV vs. orally may not be very different
      4. As Rate of Absorption ↓ …
         1. Cmax ↓
         2. Tmax ↑
         3. AUC is constant
         4. Half life is constant
            1. Note is absorption rate is significantly slower than the elimination rate constant, the elimination phase will not actually reflect the drug half life
         5. OOA and TOA are slower
         6. DOA ↑ until it doesn't reach the MEC
         7. ↓ average blood concentration
      5. Factors affecting absorption rate
         1. Physicochemical properties of the drug
         2. Site of administration
         3. Taking drugs with food, etc
         4. Formulation
            1. Rate tablet breaks up
            2. Form of crystals, particle size
            3. Brands
            4. Solubility of drug, type of salt
            5. Enteric or other coating or formulation deliberately designed to slow down the release and absorption of the drug
7. Explain the potential benefits and problems associated with extended and delayed release drug formulations
   1. Benefits
      1. Longer acting drug but at higher doses and onset of action is delayed
      2. Less frequent dosing (can maintain activity overnight)
      3. Better compliance
      4. Blood concentrations rise and fall more slowly which may reduce risk of adverse effects
   2. Problems
      1. Absorption is variable among patients
      2. Delayed onset of action
         1. Can be solved by combining rapid and slow release preps
         2. Ambien uses this method ---now have rapid onset and long DOA
            1. OOA is important for sleep aid
      3. If you slow absorption rate w/o changing the CL then the same dose may fail to reach the MEC and no effect will be seen
         1. Cmax is proportional to dose so if you decrease the absorption rate you can double the dose to double the Cmax and try and get the plasma drug concentration above the MEC
            1. This can increase the DOA because of the slower absorption
      4. If the formulation that was meant to be slowly absorbed (such a high dose) was absorped rapidly
         1. Given IV rather than orally
         2. Someone chewed a tablet
         3. Dissolved a tablet before they took it
         4. Taking it with a substance that affects how it works---alcohol
         5. ^^all these things mess with the release of the drug and can lead the drug to get to toxic levels in the plasma (DOA will still be able double that of the lower dose but would now be above the MTC)
      5. Drug abuse
         1. Prolong use of drug may make body dependent on it
         2. Hydromorphone (Palladone)—continuous opiod analgesia
            1. Alcoholic beverages cause rapid release of the drug with potentially fatal effects
8. Recognize that a single dose of a drug is not adequate treatment in many instances and multiple doses must be given to maintain plasma drug levels.
   1. Treatment periods are often needed that exceed the DOA of a single dose and multiple doses are necessary to maintain the drug concentration in the blood
   2. To maintain a constant plasma concentration
      1. Infusion rate = rate of elimination = CL•Css
   3. Infusion rate = CL•Css
   4. Css = Infusion rate/CL
   5. ***For 1st order elimination***, CL is a constant and Css will be proportional to infusion rate
   6. Css does NOT depend on the rate of absorption or the Vd
      1. RE= CL \* Css
9. Recognize that when multiple doses or infusion of drugs are given to maintain a plasma drug concentration, the rate of drug delivery must match the elimination rate and therefore only depends on the clearance and desired Css.
   1. Infusion rate = CL•Css
   2. Css = Infusion rate/CL
10. Describe the relationship between steady state plasma drug concentration and infusion rate for a drug eliminated by first order kinetics. Compare this with the relationship seen for a drug that exhibits saturable elimination. On the basis og these relationships, explain the disadvantage of administering drugs whose elimination approaches zero-order.
    1. Zero order kinetics
       1. 
       2. b/c RE= Infusion rate then…
       3. then 
       4. IMPORTANT
          1. Css rise is **not** proportional to ↑ in dose when elimination becomes saturated (approaches REmax)
          2. Css  approaches infinity as the infusion rate approaches REmax
          3. If the infusion rate exceeds REmax, Css has no real values as a steady state cannot exist (because reaction is saturated & plasma drug concentration will rise continuously)
          4. Even if the therapeutic range is the same for the two drugs, the safe and effective dosage range is much wider for a drug eliminated by 1st order kinetics than one approaching zero-order kinetics
             1. Very very narrow dose range for a drug that is governed by zero order kinetics so much easier to over or underdose a patient
11. Describe plasma drug concentration-time curve following initiation of a continuous IV infusion and the significance of rate of infusion, elimination half-life and CL to the relationship.
    1. When infusion is begun at a constant rate, plasma drug concentration (C) rises
       1. If there were no elimination, C would rise linearly
       2. If there is elimination, the increase slows down  
          and eventually a steady state is reached when  
           **rate of elimination** = **rate of infusion** 
          1. and plasma drug concentration becomes constant (Css )
    2. If elimination is first-order, the steady state concentration (Css) is proportional to the rate of infusion (b/c CL is constant)
       1. RE = CL•Css = Infusion rate
       2. If you double CL…
          1. Css ↓ by 50% but steady state is reached twice as fast since half life is inversely related to CL (increase CL shorten half life)
          2. RE ↑ and become faster than infusion rate (this is set by the doctor) so plasma drug concentration will start to fall which will lead to a consequent ↓ in the rate of drug elimination until a new Css is reached, when once again when the rate of elimination becomes equal to the rate of infusion
          3. So change in rate of elimination is transient!!
          4. Net result for a more rapid CL
             1. Css wil be lower
             2. Since CL and elimination t1/2­ are inversely --the half life of drug will be shorter and the steady state will be achieved more quickly
    3. The time taken to reach the steady state depends only on the elimination half-life/clearance (as usual, 5 x t1/2)
       1. From any point on the curve, in one half-life the concentration will rise half-way to the steady stead concentration Css so at 5 t1/2 the concentration will be 96.875% of the Css so the rule of thumb is it takes **4-5 elimination half-lives to reach a steady state**
12. Recognize that the same principles apply when multiple intermittent doses are administered by IV or other route, but that drug concentrations will fluctuate. Describe what determines the average steady state concentration and how long it takes to get there.
    1. Css is ONLY DEPENDENT on CL and INFUSION RATE (independent of Vd)
       1. But t1/2 depends on Vd (and on CL)
          1. If Vd ↑ --time to reach the steady state will be ↑
          2. If Vd ↓ --time to reach steady state will be ↓
    2. Remember
       1. Css = Infusion rate/CL
       2. t1/2= ln2\*Vd/CL = 0.69\*Vd/CL
       3. Whenever dosing/infusion rates change it takes 5X’s t1/2­ to get to the new steady state
    3. Drugs with shorter half lives will reach steady state most quickly!
    4. Do not confuse the time to get to the steady state with the time it takes to see an effect of the drug (this will depend on the MEC while time to steady state is important for monitoring)
       1. Wait until steady state to adjust dosing
13. Describe the effect of changing the dose and dosing interval on the curves and how the optimal interval is determined.
    1. Remember
       1. Css = Infusion rate/CL
       2. t1/2= ln2\*Vd/CL = 0.69\*Vd/CL
       3. Whenever dosing/infusion rates change it takes 5X’s t1/2­ to get to the new steady state
14. Recognize that the extent of the fluctuations will depend on the dosing interval, half- life, and rate of absorption relative to elimination
    1. Intermittent dosing (for patients who don't want to be hooked up to an IV)
       1. (Css)average = (Dose/dosing interval)/CL
       2. the average value of the plasma drug concentration at the steady state is proportional to the rate of drug delivery and is inversely proportional to CL
       3. takes **4-5 elimination half-lives to reach a steady state**
    2. Plasma concentrations of drug will fluctuate so…
       1. The higher the dose and longer the interval the larger the fluctuations will be
          1. Dose interval will depend on MEC and MTC and t1/2­  (CL and Vd)
             1. Remember: t½ = 0.693•Vd/CL

So if you ↑ Vd then you ↑ t1/2 ­and ↓ fluctuation and less risk of going outside the therapeutic range

So if you ↓ Vd then you ↓ t1/2 ­and ↑ fluctuation and more risk of going outside the therapeutic range

So if you have a larger Vd you will have less fluctuations which allows you to increase the dosing rate (ex: from 100units/day to 200 units/2 days)

* + - * 1. Vd has NO effect on steady state level but does effect the time it takes to get to the steady state b/c it effects t1/2 Steady state Css depends only on dose rate and CL

Magnitude of Vd has **no effect Css**

***However,***

***M***agnitude of Css fluctuations depends on Vd; a lower Vd → shorter t½ and larger fluctuations and greater risk of going outside therapeutic range

Also the time to reach steady state proportional to Vd

***What factors affect Vd?***

Lipophilicity of drug (PC)

Body size/weight

Ratio of fat/lean body mass, plasma protein binding

* + - 1. Drugs with narrow therapeutic window/range will require more frequent dosing of smaller doses
    1. Summary
       1. Fluctuations will ↑ if the dosing interval is ↑ and if the rate of absorption (*ka*) is ↑ and will be larger for drugs with ↓ Vd
  1. Oral Dosing
     1. Same principles apply 🡪 (Css)average = (Dose/dosing interval)/CL
        1. Average Css  depends on CL and administration rate
     2. Main difference between oral vs. IV dosing is the **slower absorption** which ↓ the peak plasma concentration (which smoothes the fluctuations)
     3. Although it takes 4-5 half-lives to reach a steady state, it may not take that long to see a clinical effect, since that depends on the MEC

1. Describe what is meant by and purpose of a “loading dose”.
   1. For drugs eliminated slowly, it can take a long time to reach a steady state in the therapeutic range
      1. Ex: a drug with a half life of 2 weeks will take 10 weeks to reach a steady state
      2. **The time taken to reach the therapeutic range can be ↓ by administering a “loading dose” –a dose that is larger than the maintenance dose**
      3. Loading doses can be useful for drugs that are eliminated slowly in order to get into the therapeutic range more quickly
      4. Most frequently, the loading dose is determined using the formula: LD = [Desired Plasma Drug Conc] x VD
2. Explain that loading doses may be calculated from half-life and Vd for infusions, intermittent injections and oral doses. Calculate loading doses for the simplest cases.
   1. Method 1 (IV Bolus)
      1. Loading Dose = Css • Vd
      2. Prior to beginning infusion
      3. ***Object*:** Aim for the peak (Css)max
         1. LD is calculated from the maintenance dose (MD)
         2. Basic formula:
            1. 
            2. 

*LD* = *MD* • Accumulation factor

*Accumulation factor* (amount of drug in the body at the peak/MD)

* + - * 1. If Δt (dosing interval) = t½, it follows that🡪 ***LD* = 2 • *MD***
        2. It can be shown that

(Css)max  Vd = MD/(1-exp(-keΔt))

= MD  Accumulation factor

where Δt is the selected dosing interval

Note that the term 1/(1-exp(-keΔt)) is sometimes referred to as the “**accumulation factor**” as it is the ratio of ((Css)max  Vd)/MD, i.e. (the amount of drug in the body at the peak)/MD

* + - * 1. Since, ke = ln2/t1⁄2--this can be simplified

LD = MD/(1-exp(-ln2t/t1⁄2))

* + - * 1. Since exp(-ln2) = 0.5, this can be further simplified to

LD = MD/(1-0.5^(Δt/t1⁄2))

* + - * 1. Finally, if dosing interval (Δt) is set to equal the t1⁄2, then..

Δt/t1⁄2 = 1 & 0.51 = 0.5 so 1-0.5 = 0.5

LD= MD/0.5 OR

LD= 2\*MD

\*\*only true if the loading interval is equal to the half life

* + - 1. IMPORTANT CONCLUSIONS
         1. The loading dose depends on the Vd and it can be calculated from the  maintenance dose (MD) and the dosing interval: half-life ratio.
         2. If the dosing interval is set to equal the half-life, the loading dose is simply twice the maintenance dose
      2. ***IMPORTANT NOTE:* This discussion assumes that drug distribution is very rapid. If it is not, the initial peak may be much higher than (Css)max and may exceed the MTC.** 
         1. **Thus, IV loading doses must be given very cautiously and often slowly to avoid toxic effects.**
  1. Method 2 (DOUBLE INFUSION RATE)
     1. **AIM FOR Css**
     2. Give a loading dose that is equal to the average total amount of drug in the body at the steady state
     3. Start infusion at 2 x’s desired Maintenance rate (double the maintenance rate)
     4. Desired Css will be reached in one half-life
     5. At one half-life, switch to maintenance rate
     6. STEPS
        1. Loading Dose = (Css)average • Vd
        2. 
     7. Important Conclusions
        1. This LD falls short of the steady state value, however its calculation is independent of MD and dosing interval
        2. Risk of adverse effects will however be lower and will likely get the drug concentration into the therapeutic range as quickly
  2. Same principles apply to oral or other routes of administration
     1. Since absorption must take place the risk of exceeding the MTC due to relatively slow distribution is much less likely compared with IV administration

1. Recognize potential dangers of administering an IV loading dose.
   1. **If rate of distribution is slow relative to rate of absorption**, e.g. IV administration, a loading dose may lead to toxic concentrations in the blood

\*\*What does half life tell us??

* 1) How long it takes to get to a steady state plasma concentration after initiating therapy (4-5)
* 2)  How long it takes to get to a new steady state after the dose is increased or decreased (4-5)
* 3)  How long it takes to eliminate a drug from the body
* 4)  It is also important in calculating the loading dose